Environmental and Genetic Risk Factors and Gene–Environment Interactions in the Pathogenesis of Chronic Obstructive Lung Disease

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Current understanding of the pathogenesis of chronic obstructive pulmonary disease (COPD), a source of substantial morbidity and mortality in the United States, suggests that chronic inflammation leads to the airways obstruction and parenchymal destruction that characterize this condition. Environmental factors, especially tobacco smoke exposure, are known to accelerate longitudinal decline of lung function, and there is substantial evidence that upregulation of inflammatory pathways plays a vital role in this process. Genetic regulation of both inflammatory responses and anti-inflammatory protective mechanisms likely underlies the heritability of COPD observed in family studies. In alpha-1 protease inhibitor deficiency, the only genetic disorder known to cause COPD, lack of inhibition of elastase activity, results in the parenchymal destruction of emphysema. Other genetic polymorphisms have been hypothesized to alter the risk of COPD but have not been established as causes of this condition. It is likely that multiple genetic factors interacting with each other and with a number of environmental agents will be found to result in the development of COPD. *Key words*: air pollution, alpha-1 antitrypsin, environment, genetics, lung disease, obstructive, occupational diseases. — *Environ Health Perspect* 108(suppl 4):733–742 (2000).
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Tobacco smoking and occupational dust exposure are environmental risk factors for the development of chronic obstructive pulmonary disease (COPD). Only a minority of exposed persons, however, develops disabling COPD; this does not appear related only to cumulative exposure. At least one genetic disorder, homozygous alpha-1 protease inhibitor (API) deficiency, is known to cause COPD; recent reports suggest that other genetic factors may also predispose to this condition. These observations suggest genetically determined characteristics, particularly those influencing the modulation of inflammatory injury, likely interact with environmental factors in the pathogenesis of COPD. The environmental and genetic risk factors for COPD, and the interaction between them, are the focus of this review.

Definition and Pathophysiology of COPD

Chronic obstructive pulmonary disease affects more than 10% of the U.S. adult population (*1,2*). It is the fourth leading cause of death in the United States, accounting for over 100,000 deaths per year, and it is the second leading diagnosis for Social Security disability payment recipients (*3*). COPD can be defined as chronic and mostly irreversible airflow limitation; conditions such as obstructing lesions of the central airways and bronchiectasis or cystic fibrosis are specifically excluded (*4*). Chronic bronchitis, defined as chronic mucous hypersecretion leading to productive cough (*4*), often coexists with chronic airflow obstruction and is generally considered part of the spectrum of COPD. Most of the morbidity and mortality caused by COPD, however, results from the chronic airflow obstruction and associated gas exchange and hemodynamic abnormalities rather than from the mucous hypersecretion (*5,6*). The primarily irreversible airflow limitation of COPD distinguishes it from asthma, which is characterized, at least in its early stages, by variable and largely reversible airflow limitation.

The defining physiologic characteristic of COPD is airflow obstruction on spirometry, i.e., a reduction in both FEV_1 (the forced expiratory volume in 1 sec) and the FEV_1/FVC (forced vital capacity) ratio. The airflow obstruction develops gradually and progressively over many years (*7*). The eventual development of disabling COPD may result both from processes affecting lung growth and development in early life and from processes affecting longitudinal pulmonary function decline in adulthood (*8,9*). As the chronic airflow obstruction of COPD progresses, it may be accompanied by hyperinflation of the chest (physiologically measured as an increased total lung capacity) due to both gas trapping (physiologically measured as an increased residual volume) and loss of elastic recoil. These changes may eventually put the muscles of respiration at a mechanical disadvantage, with the resultant respiratory muscle dysfunction further worsening dyspnea, the cardinal symptom of COPD, and compromising functional status. Progressive worsening of ventilatory function ultimately leads to impaired gas exchange, with resultant hypoxemia and hypercapnia.

The histopathologic changes underlying the chronic airflow obstruction of COPD include both pulmonary emphysema and inflammatory disease of the small airways (*10*). Emphysema is defined as abnormal enlargement of the alveolar airspaces caused by the destruction of the alveolar walls. This parenchymal destruction results in the reduction in alveolar attachments tethering open the bronchioles and the obliteration of functional alveolar–capillary units for gas exchange. In addition to emphysema, lung tissue from patients with COPD shows inflammation of the small airways (i.e., the bronchi with a diameter less than 2 mm and the bronchioles), with increased numbers of macrophages and neutrophils, goblet cell metaplasia, mucus plugging, and fibrosis. The loss of radial traction on the peripheral airways, due to the destruction of alveolar attachments, and the thickened bronchial walls, due to bronchiolitis, result in reduction in the radius of the airways and a consequent increase in airways resistance. There has been controversy about the relative contributions of parenchymal and airways disease to the airflow obstruction of COPD (*11,12*), although these two abnormalities are not independent inasmuch as the degree of small airways disease has been associated with the loss of alveolar attachment (*13,14*). Although it seems clear that emphysema is often the major histopathologic abnormality for patients with severe COPD, small airways disease probably makes an important contribution and may be the major pathologic abnormality in some patients.

The cellular and molecular mechanisms involved in the development of the airflow obstruction of COPD are not fully understood, and substantial heterogeneity in the pathogenesis of COPD likely exists. A model for understanding the development of this disease has emerged, however, from investigations of the major environmental risk factor for COPD (tobacco smoking)

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and of the most clearly understood genetic risk factor (API deficiency). In this model of COPD pathogenesis, the maintenance of healthy lung structure and function depends on the ability of homeostatic mechanisms to protect the airways and lung parenchyma from both environmental insults and the inflammatory responses to these insults (*10*). Chronic airflow obstruction can develop because of a high degree of chronic inflammation or other injurious process, a deficiency in protective mechanisms, or both. Lung antiproteases, which modulate proteolytic enzymes released by inflammatory cells and thereby prevent damage at sites of inflammatory response, appear to be crucial in this balance (*10,15*), as discussed below. Antioxidants and other less well understood protective mechanisms may also be important in preserving normal lung function in the face of a lifetime of exposure to potentially injurious environmental factors.

Environmental Risk Factors

A variety of environmental factors have been associated, both positively and negatively, with changes in lung function (Table 1). Myriad exposures, including workplace, atmospheric, domestic, dietary, and others, play putative roles in altering lung function. Those exposures, and the hypothesized mechanisms through which they impact lung function, are reviewed below.

Tobacco smoking is the best-documented environmental cause of chronic airflow obstruction and is implicated in more than 90% of COPD cases (*16*). In cross-sectional surveys, smoking history is strongly associated with chronic respiratory symptoms, diagnosed chronic bronchitis and emphysema, and obstructive pulmonary function abnormalities (*9*). Cohort studies have revealed that adult smokers experience faster longitudinal pulmonary function decline than nonsmokers (*7,17*) and that this accelerated decline returns to the normal rate of aging-related decline following smoking cessation (*9,18*), even if the cessation is intermittent (*19*). In addition, smoking has an adverse impact on lung function and growth and on the peak pulmonary function attained among those who take up the habit early. Smoking teenagers experience a reduced rate of lung function growth, and young adult smokers experience an earlier onset of pulmonary function decline from the plateau of maximal function achieved in the third decade of life (*20*).

Table 1. Environmental factors influencing the risk of COPD.

Agent	Established	Suspected
Tobacco	Active smoking	Environmental tobacco smoke
Biologic dusts	Grain	Cotton Cork/wood/paper
Inorganic dusts	Silica (gold and coal mining)	Chalk Talc
Fumes, gases		Metal Chlorine SO_2 H_2S, styrene, polyvinyl chloride/methyl Methacrylate
Pollution		Particulate NO_2 SO_2 O_3^- Biologic cooking fuels
Dietary factors		Antioxidant vitamins, especially A, C, E (appear to be protective) Linoleic acid Fish oils (appear to be protective) Ethanol (effect mixed)

The mechanisms by which tobacco smoking causes COPD have been the subject of considerable investigation. Substantial evidence suggests the accelerated decline of lung function in cigarette smokers results from smoke-induced inflammatory processes. Inflammation begins with an increased numbers of macrophages in the first- and second-generation respiratory bronchioles, where centrilobular emphysema begins (*21*). Ultimately, it extends throughout the bronchial tree, with the macrophage predominance of the smallest airways changing to lymphocyte predominance in medium and large airways (*22–25*). The lungs of cigarette smokers (*26–29*), as well as the peripheral blood, contain markedly elevated numbers of neutrophils, and blood leukocyte count correlates with the level and rate of decline of FEV_1 and FVC after adjustment for smoking status (*30,31*). Centrilobular emphysema and small airway disease, both of which are important in the pathophysiology of airflow obstruction (*32*), appear to be the result of small airways inflammation.

Neutrophils and macrophages produce, respectively, human neutrophil elastase (HNE) and metalloelastases; these proteolytic enzymes have been implicated in the parenchymal destruction that results in emphysema. Individuals with severe deficiency of API, the major inhibitor of HNE activity, experience premature development of emphysema (*10*), as discussed in more detail below. Elastase (*33,34*) and elastase–API complexes (*35*) are found in higher concentrations in the bronchoalveolar lavage fluid of smokers. The plasma of COPD patients contains elevated levels of elastin-derived peptides compared with that of nonsmokers (*36,37*). Intratracheal instillation of proteases with elastolytic activity provides an animal model for emphysema (*38*). Proteases and protease inhibitors may also play a role in the pathogenesis of small airway disease. In addition to the degradation of airway elastin, HNE and API have, respectively, pro- and anti-inflammatory effects (*39,40*). Increased elastin degradation has been observed in smokers with rapid decline in lung function, an effect seen equally in subjects with predominantly emphysema and those with predominantly airway disease (*41*).

Oxidative injury may also play an important role in the pathogenesis of COPD (*42*). Such injury, resulting from an imbalance between free radicals and protective mechanisms, can alter the protein conformation of protease inhibitors and reparative enzymes, injure cell membranes, and result in mutagenesis. Free radicals appear in the lung by inhalation from the environment or by release from inflammatory cells. Tobacco smoke contains a heavy oxidative burden for the lungs, both in the gas phase and in the tar components (*43*), and causes a transient decline in the antioxidant capacity 1 hr after smoking a single cigarette (*44,45*). Both current smoking and COPD exacerbations are associated with increased levels of markers of oxidative stress and decreased levels of serum antioxidants (*44,45*). Depletion of the buffer against free radicals, either as a result of a heavy free radical burden or of a decreased antioxidant capacity, may alter the protease/antiprotease balance by inactivation of antiproteases (*46*), thereby contributing to the pathogenesis of COPD.

Passive exposure to environmental tobacco smoke (ETS) has been hypothesized to be a risk factor for the development of COPD, but this question has not been answered with certainty. Dose–response curves in smokers, measured in terms of pack-years and reduction in FEV_1, suggest that the estimated ETS exposure of nonsmokers living and working with smokers may be sufficient to contribute to the development of airflow limitation (*47*). The composition of unfiltered sidestream tobacco smoke differs in component concentrations from that of smoke inhaled directly during active smoking, as it contains higher concentrations of some toxins (*43,47*). Studies of airflow obstruction and ETS in adults are complicated by the difficulties of assessing lifetime cumulative ETS exposure, accounting for other respiratory irritants, and ascertaining any active smoking in the past. Evidence definitively linking ETS exposure to chronic airflow obstruction in adults is lacking because of methodologic difficulties with existing studies (*47,48*). There is a consensus, however, that passive exposure is associated with reduced pulmonary function in children. A longitudinal study by Tager et al. (*49*) demonstrated a 10.7% reduction in

FEV_1 among children with a parent that smoked compared to children of a nonsmoker. It has been estimated that ETS exposure in childhood results in a 0.5% FEV_1/year decrease in growth of FEV_1 (*50*). This reduction of maximally attained function is hypothesized to predispose to impairment of pulmonary function in later life (*51*).

Occupational exposure to biologic dusts has been established as a risk factor for COPD (*52*). Grain dust exposure has been linked to chronic airflow obstruction in both cross-sectional (*53–59*) and longitudinal (*60,61*) studies, an association that appears to be independent of the effects of tobacco smoking. The chronic airflow obstruction caused by grain dust exposure does not appear to be associated with either airway hyperreactivity or allergy to grain constituents (*62–64*). Cotton dust exposure in the workplace has been reported to be associated with accelerated longitudinal lung function decline (*65*), but not all studies confirm these findings (*66*). Although acute byssinosis of cotton dust appears to be caused by the stimulation of endotoxin-mediated inflammatory mechanisms, it is not clear that endotoxin is responsible for the chronic airflow obstruction caused by long-term cotton dust exposure. The longest cohort study of cotton workers demonstrated an excess longitudinal decline of FEV_1, compared to silk workers, most pronounced in the early years of exposure; loss of pulmonary function was independent of estimated exposure to inhaled endotoxin (*65*). Other workplace biologic dusts implicated in the development of chronic airflow obstruction include cork (*67*), wood (*68*), sugar (*69*), and paper dusts (*70*).

Exposure to certain inorganic dusts in mining and other occupations has also been shown to be a risk factor for the development of chronic airflow obstruction independent of smoking and pneumoconiosis (*71–73*). A meta-analysis (*74*) of studies of coal and gold miners demonstrated that airflow obstruction was common, more so in gold miners than coal miners. Silica has been implicated in the development of airflow obstruction (*75*) and the difference between gold miners and coal miners may be the result of higher silica exposure in the former group. Occupational chalk dust (*69*) and talc (*76*) exposure have also been reported to be associated with chronic airflow obstruction.

Although the mechanisms by which biologic and inorganic dusts lead to chronic airflow obstruction are not fully understood, many of the same mechanisms underlying the development of airflow obstruction from tobacco exposure may be involved. Particle deposition in the small airways may induce inflammatory responses, which lead to chronic airway changes as well as the development of centrilobular emphysema, as described above in relation to tobacco smoke. Dust-exposed groups have been noted to have goblet cell metaplasia and fibrosis of the membranous bronchioles beyond that seen in smokers (*77*). These changes were not seen in other portions of the bronchial tree.

Occupational exposure to chemical fumes and gases has also been linked to chronic airflow obstruction. Metal fumes, a product of metal working in a variety of industries, are associated with impairment of lung function. Welders and those exposed to metal fumes have been noted to have a lower FEV_1 (*78–82*), and the duration of exposure is significantly related to the reduction of lung function (*82*). Indirect measures of metal buildup in the lungs correlate with the severity of lung function impairment (*78*).

Chlorine in various forms is used in many industries and frequently appears with other irritant gases. Pulp and paper mill workers, frequently exposed to chlorine and SO_2 gases, have been reported to have a high prevalence of chronic airflow obstruction (*70,79,83,84*). The degree of airflow limitation is directly related to the degree of exposure, and there is at least an additive effect of smoking (*84,85*). Chlorine bleach, which frequently induces respiratory symptoms, has also been associated with a decline in lung function (*70*), even with minimal history of tobacco use (*84*).

Chronic airflow obstruction has also been reported in association with long-term exposure to H_2S (*86*), styrene and methyl methacrylate (*87*), and polyvinyl chloride (*88*). Fiberglass and modern insulation materials have inconsistent impact on airflow (*80,89*). For these various gases and fumes encountered in the workplace, the molecular and cellular mechanisms leading to chronic airflow obstruction remain uncertain, although direct chemical injury to the airway epithelium may be the initial event in the pathogenesis of airflow obstruction.

Outdoor air pollution is a hypothesized but unproven risk factor for the development of COPD (*90*). Although the relative independent contribution of individual pollutants remains uncertain (*91*), studies of the acute effects of air pollution suggest that episodic increases in particulate matter (*92–95*), NO_2 (*95,96*), SO_2 (*95,97,98*), and ozone (*92,94–96,99,100*) may cause increased respiratory symptoms and hospitalizations among persons with COPD. Less is known about the long-term effects of air pollution on pulmonary function. Although some cross-sectional studies have revealed lower mean pulmonary function levels and a higher prevalence of airflow obstruction among adults living in more polluted communities (*101–105*), other studies revealed no such differences between communities (*106,107*). Studies of air pollution and lung function in children revealed lower levels of lung function (*108*) in children living in communities with higher levels of NO_2, O_3^-, and particulate matter. The relation between lung function and SO_2 in children is less clear (*108*). Living in close proximity to a major point source of industrial emissions has been reported to be a risk factor for pulmonary functional impairment among children (*109*).

Cohort studies suggest that the rate of longitudinal lung function decline in adults is related to ambient air pollution levels (*105*). These studies, however, must be interpreted with caution because of potential imprecision in estimating pollution exposure as well as possible confounding factors. The quantitative impact of particular pollutants on pulmonary function is not fully understood, but dose–response relationships have been demonstrated in several studies (*103,110*), further suggesting an impact of air pollution on long-term lung function.

The combustion of heating and cooking fuels in indoor environments leads to the pollution of indoor air with respirable particles, nitrogen dioxide, and other pollutants. Although the contribution of these indoor pollutants to the risk of developing COPD is difficult to quantitate, several studies suggest a relation between indoor fuel combustion practices and COPD risk (*111–115*). Exposure to indoor air pollution caused by fuel combustion is greater in poorer nations, and the potential health impact may vary accordingly.

The environment is not always inhospitable; some factors may help preserve pulmonary function and prevent COPD. The role of diet in the pathogenesis of lung disease is not clear, but as our understanding of the pathogenesis of COPD evolves, the potential role of diet increases. Antioxidant vitamins (including C and E) may provide a protective benefit, but the evidence remains controversial (*116,117*). Vitamin E treatment of children of smokers reduced the susceptibility to red blood cell peroxidation *in vitro* (*118*). Certain fatty acids that affect arachidonic acid metabolism, such as linoleic acid, may worsen pulmonary function (*119*), whereas intake of others (such as fish oils) may be protective (*120,121*), but the effects of these dietary factors were modest. Investigations into the effects of ethanol have demonstrated mixed results. Cross-sectional analysis of an ongoing cohort study demonstrated no difference between the pulmonary function of heavy drinkers once adjustments were made for confounding factors (*122*). Others have found a small protective effect (*123*), even with moderate alcohol consumption (*119*). Any impact of alcohol on airflow obstruction, once adjusted for smoking status, is likely to be modest.

Vitamin A and its derivatives represent an especially promising venue of research. Massaro and Massaro (*124*) observed that rodents with elastase-induced emphysema treated with vitamin A derivatives had reversal of the injury pattern, nearly normalizing all measured indices of emphysema. In humans, a small study noted that COPD patients had low vitamin A status, independent of smoking, and that treatment with vitamin A reversed airways obstruction (*125*). Further study of the effects of vitamin A derivatives on pulmonary emphysema is ongoing.

Because inflammation plays a key role in the pathogenesis of COPD, it is possible that chronic or recurrent infections during adulthood result in the development or progression of this condition. This hypothesis, which was advanced by British investigators in the 1960s and came to be known as the "British hypothesis," has not been supported by epidemiologic investigations (*126*). Published data do suggest that viral lower respiratory infections during childhood may predispose to impairment of pulmonary function in later life, possibly thereby increasing the risk of COPD (*127*).

Genetic Factors

A number of studies demonstrate a strong familial correlation of pulmonary function measurements (*128–137*). The degree of correlation of FEV_1 or FVC, adjusted for age, smoking habits, and body habitus, has been reported to be in the range of 0.11–0.40 for relatives with 50% genetic identity, with values typically between 0.20 and 0.25 (*132–137*). Using path analysis to estimate the relative contributions of environmental and genetic factors in determining level of lung function, two groups concluded that 42–45% of FEV_1 variability was due to heritable factors (*129,134*). These heritability estimates are consistent with the finding of Redline et al. (*132*) that the correlation of FEV_1 was 0.71 among 252 adult monozygotic twins. Two studies that used segregation analysis revealed a pattern of familial correlation of pulmonary function consistent with a polygenic, rather than a single major Mendelian gene, mode of transmission; these models, however, could not exclude familial environmental rather than genetic factors (*135,136*). Rybicki et al. (*133*) examined 85 COPD families and 56 non-COPD families for evidence of Mendelian transmission in the expression of FEV_1, and found evidence of a co-dominant major gene among the COPD families but not among non-COPD families. Although these studies suggest a role for genetic factors in determining airflow, most describe lung function in generally healthy subjects, and their relevance to clinical COPD is uncertain.

Several studies have provided direct evidence of familial clustering of COPD (*138–141*). These studies observed a higher prevalence of COPD among relatives of COPD patients than among relatives of control subjects without lung disease. Among smoking siblings of COPD patients, the relative risk of chronic airflow obstruction was in the range of 2 (*139*) to 4 (*140*) compared to smokers without a family history of COPD. Thus, multiple studies in diverse populations consistently have shown strong evidence for heritability of lung function and familial aggregation of COPD after adjustment for smoking status, and it appears likely that multiple genes are involved.

API deficiency is the only known genetic disorder unequivocally implicated as a cause of emphysema, although only a small proportion of COPD cases can be attributed to this condition. API, an antiprotease that inhibits the activity of neutrophil elastase and other proteolytic enzymes, is a serum protein primarily synthesized in the liver, mononuclear phagocytes, neutrophils, bowel, and kidney (*142,143*). The gene encoding API, located on chromosomal segment 14q32.1, is highly pleomorphic, and over 75 distinct alleles have been described (*142*). The Pi-M allele and its subtypes are the most common, with a gene frequency of approximately 900 in 1,000; persons with Pi-MM genotype have normal serum levels of normally functioning API. The Pi-Z allele has a point mutation in exon V that impairs secretion of synthesized API protein (*144*), and Pi-ZZ homozygotes have extremely low serum levels of normally functioning API. The Pi-ZZ genotype is the most common genotype among persons with severe API deficiency. The Pi-S allele is associated with reduced serum levels of API but to a lesser extent than Pi-Z, and persons with the Pi-SS genotype have serum API levels intermediate between those of persons with Pi-MM and Pi-ZZ. Nonexpressing null alleles are associated with the absence of API synthesis, and the Pi-null null and Pi-Z null genotypes are also associated with severe API deficiency. The API phenotype, assessed by the distinct electrophoretic patterns associated with different alleles, is often used as a surrogate for genotype.

Persons with severe API deficiency (usually Pi-ZZ, rarely Pi-Z null or Pi-null null) often develop severe emphysema at a relatively early age, and this is the major cause of morbidity and mortality in this condition (*145*). Pulmonary development and growth in early life appear normal, and lung function remains in the normal range in adolescence and the beginning of young adulthood. Early in adulthood, persons with severe API deficiency begin to develop emphysema due to lack of inhibition of lung connective tissue degradation by neutrophil elastase and other proteases. Even among never smokers, longitudinal studies demonstrate excessive loss (47–86 mL/year) of FEV_1 (*146*) compared to historical controls (20–30 mL/year). As discussed in detail later, emphysema develops even more quickly in smokers with API deficiency. The emphysema associated with API deficiency has a pan-acinar pathologic pattern, a feature distinguishing it from the centrilobular pattern typical of smoking-induced emphysema absent API deficiency (*147*). Emphysema, when present in severe API deficiency (Pi-Z), includes the lung bases in the overwhelming majority of cases (*142*) and has been suggested as a distinctive feature of this disorder.

Fewer than 1 in 1,600 U.S. Caucasians and even fewer non-Caucasians are estimated to have the Pi-ZZ genotype, so only a small minority of cases of COPD can be attributed to severe API deficiency related to this genotype. There is continuing controversy about the possibility that milder degrees of API deficiency, such as that associated with the Pi-MZ genotype, may be associated with increased risk of developing chronic airflow obstruction. A number of early studies suggested that the Pi-MZ genotype occurs in greater than expected frequency among patients with emphysema (*148–152*). A post mortem study found that emphysema was more prevalent than expected among those with mild API deficiency (*153*). Some of these early studies, however, inferred the API genotype from serum API levels, which may have resulted in misclassification of Pi-MZ and Pi-MM patients (*154*). Case–control studies, as summarized by Sandford et al. (*155*) have suggested a 2- to 4-fold increased odds of COPD in Pi-MZ heterozygotes.

In contrast to these case–control studies, population-based studies have generally indicated little association between the Pi-MZ phenotype and impairment of pulmonary function when controlling for smoking status. Cross-sectional analysis of 143 Pi-MZ subjects showed similar pulmonary function (spirometry, diffusion, and lung volumes) compared to matched controls (*154*). A 3-year longitudinal study of Pi-MZ patients did not demonstrate excess decline of FEV_1 or FVC when compared to controls matched for age, sex, height, race, and tobacco use (*143*). These studies, however, are not without limitations and it has been proposed that Pi-MZ patients self-select away from exposures that would result in impaired pulmonary physiology (*156*). Other studies have revealed subtle abnormalities of pulmonary function in association with the Pi-MZ genotype, including alterations in pressure/volume curves (*157*).

Even among persons with normal baseline serum levels of API, genetic variation impairing the upregulation of API during stress may confer increased susceptibility to COPD. In one study, a polymorphism in the 3′ flanking region of the API gene has been reported to be present in 17% of patients with COPD but in only 5% of the general population of the United Kingdom (*158*). Although it is not associated with abnormal API serum level or function, it has been suggested that this polymorphism lies within an enhancer sequence and may impair the acute phase increase in API expression (*158,159*).

Much less is known about the possible role of other protease inhibitor genes in the pathogenesis of COPD. The protease inhibitor α_1-antichymotrypsin (ACT) is the major physiologic inhibitor of cathepsin G, an elastolytic protease produced by neutrophils, and has been observed to be protective against pancreatitis-induced lung injury in rats (*160*). The gene encoding ACT is located on chromosome 14, in close proximity to the API gene (*161*). Two mutations of the ACT gene were identified in a screening study of 200 COPD patients of German extraction and were associated in heterozygotes with a reduction in serum ACT activity to 62–75% of normal (*162,163*). These mutations were present in 1.5 and 4%, respectively, of patients with COPD but in none of 100 control subjects. This association of COPD and ACT mutations was not duplicated in other trials (*164*). α_2-Macroglobulin is a serum nonspecific antiprotease that appears in the sputum during infections (*165*). Genetic variation in the ACT structure has been associated with premature lung disease (*166,167*), but these findings have not been consistently replicated and the role of α_2-macroglobulin in lung disease remains unclear (*168*). Other antiproteases, including serum leukoprotease inhibitor and elafin, have been proposed as playing a role in COPD pathogenesis (*169*), but their importance in the development of COPD remains speculative.

The hypothesis that an imbalance between protease and antiprotease activity plays a key role in COPD pathogenesis suggests that genetically determined variations of protease expression could predispose to or protect from COPD. A knockout mouse lacking macrophage metalloelastases does not develop emphysema in response to tobacco smoke exposure as do its wild-type counterparts (*170*). Conversely, a transgenic rat expressing human collagenase has been observed spontaneously to develop emphysema (*171*). Patients with emphysema have increased levels of collagenase (MMP-1) and gelatinase-B (MMP-9), and have alveolar macrophages that express more MMP-9 and MMP-1 compared to controls (*172*). Other proteases of potential importance in the pathogenesis of COPD include other matrix metalloproteinases and lysosomal cathepsins; there are no data, however, to indicate that genetics controlling the levels of these proteases differ between emphysema patients and controls. Additionally, there are no human data linking mutations of the genes encoding these proteases to the development of COPD.

Other immunologic factors have been reported to be associated with COPD. One study of human leukocyte antigen expression found a greater prevalence of Bw16 antigen and a lower prevalence of B7 antigen in persons with COPD than in healthy controls (*173*), although these findings have not been reproduced. Various immunoglobulin deficiencies of IgG subtypes and IgA have been described in association with COPD (*174–178*). Vitamin D binding protein is a multifunctional protein that, in addition to binding vitamin D, enhances the effects of chemotactic factors (*179–182*). Isoforms of the protein have been found with decreased (*140*) or increased frequency (*183,184*) in COPD patients, although the results have been inconsistent (*173*).

A variety of other mediators of inflammation may play a role in the pathogenesis of COPD, though the understanding of their contributions remains in its infancy. The role of lymphocyte response, and mediators thereof, are under investigation. Lymphocytes appear to respond through TH-1 (*185*) mechanisms, and work on describing the mediators of this response has begun (*186,187*). Variation in certain mediators of inflammation, including tumor necrosis factor alpha and interleukin (IL)-8 (*188*), have also been found in COPD subpopulations, and IL-4 receptor blockade has been associated with a reduction in neutrophil survival (*189*). A positive association between pulmonary surfactant and airways diameter has been described; surfactant proteins were observed to inhibit pulmonary inflammation (*190*). Production of particular surfactant proteins is inhibited by tobacco smoking (*191*). Linking of these observations in the pathogenesis of COPD has yet to be reported As genetic polymorphisms influencing expression or function of these and other components of the inflammatory cascade are discovered, their possible roles in the differential sensitivities to the development of COPD will be better understood.

An association between the presence of blood type A and COPD has been reported (*192–194*), but others have failed to confirm this relationship (*195,196*). Many but not all people secrete the ABO blood group antigen into the upper and lower respiratory tract, and secretor status has inconsistently been associated with airflow limitation (*168,169,197*). Lewis blood group and Lewis antigen secretor status have also been reported to be associated with airflow limitation (*198,199*). In the absence of a consistent association with COPD, or a clear biologic rationale for such an association, the roles, if any, of blood antigen specificity and secretor status in the pathogenesis of COPD remain uncertain.

Genetic factors likely affect susceptibility to oxidative injury. Metabolic processes that are upregulated in response to proinflammatory stimulants (including electron transport in the mitochondria, enzymatic activity such as cyclooxygenase, and phagocytic activity in the white blood cells) generate part of the oxidative burden to the lung. Oxidants, as discussed above, may then damage the airways, resulting in chronic airflow obstruction. Lower levels of antioxidants have been correlated with airflow obstruction (*200*). Urinary excretion of isoprostane$_{2\alpha}$III, a purported stable marker of oxidative stress, is increased in COPD patients (*201*). Microsomal epoxide hydrolase (mEPHX), which detoxifies epoxides directly, has four described alleles. Weakened defenses to oxidative stress may occur through isomeric variation; Smith and Harrison (*202*) described a higher frequency of slow mEPHX enzyme among COPD patients that may expose the lungs to unscavenged free radicals. Oxidative balance has thus been implicated in the pathogenesis of COPD, but the role of the host in generating oxidative stress and balancing protective mechanisms needs further investigation.

Gene–Environment Interactions

Tobacco smoke exposure is the strongest environmental risk factor for COPD, but only about 15% of smokers develop the disease (*52,203*), and only 25–30% of smokers of 30 pack-years or more develop clinically apparent airflow obstruction (*204,205*). Even in the presence of small airways disease indicated by a reduced FEF_{25-75} (forced expiratory flow 25–75% of vital capacity), some smokers do not develop clinically significant airflow obstruction despite ongoing smoking for may years (*206*). A recent family study compared the lung function of first-degree relatives of probands with early-onset COPD, none of whom had the Pi-ZZ genotype, to those of persons without a family history of COPD (*207*). Among nonsmokers, lung function was similar between subjects with and without a relative with COPD. Among cigarette smokers, however, relatives of a person with COPD had a mean reduction of 13% in FEV_1 compared to subjects without a family history of smoking. These epidemiologic observations suggest that host characteristics, including genes, are important determinants of susceptibility to airflow obstruction caused by environmental factors such as tobacco smoke.

The best-characterized example of gene–environment interaction in the pathogenesis of COPD is the interaction between severe API deficiency and tobacco smoking. As described above, severe API deficiency in persons with the Pi-ZZ genotype or other more rare genotypes, is associated with the premature development of severe emphysema. Among persons with severe API deficiency, those who smoke tobacco experience a more rapid rate of longitudinal lung function decline and more severe airflow obstruction than nonsmokers (*146,208*). A study from Sweden demonstrated that only 50% of Pi-ZZ smokers survived beyond 35 years of age, whereas Pi-ZZ nonsmokers had a 50% probability of surviving beyond age 57 (*145*).

The example of genetically determined API deficiency predisposing to smoking-induced chronic airflow obstruction provides a paradigm of gene-environment interaction, consistent with current hypotheses concerning the pathogenesis of COPD. In this model, an inhaled environmental agent such as tobacco smoke induces an inflammatory response in the small airways that may result in irreversible damage to the small airways and centrilobular alveoli. This damage is mediated by proteolytic enzymes and oxygen free radicals, and the degree of damage depends on genetically controlled systems that modulate the inflammatory response and protect the lung from proteolytic and oxidant injury.

Another example of possible gene–environment interaction is the hypothesized interaction between cigarette smoking and the intermediate degree of API deficiency found in heterozygotes with the Pi-MZ genotype. The putative role of the Pi-MZ genotype in the pathogenesis of COPD remains controversial; however, some reports suggest the possibility of an interaction between the Pi-MZ genotype and environmental exposures. Abnormalities of pulmonary function including abnormalities of airflow have been observed in heterozygotes who smoke (*209,210*) or have occupational exposures (*211*), although the clinical significance of these observations remains controversial. Smokers with Pi-MZ have been noted to have loss of elastic recoil, large residual volume, and increased closing capacity but not airflow obstruction (*212*). Grain workers with the Pi-MZ genotype have been reported to have a similar prevalence of respiratory or atopic symptoms but more obstructive physiology than their Pi-MM counterparts (*211*). In one study that demonstrated subtle changes in pulmonary function in association with the Pi-MZ phenotype, a subgroup analysis of six older heavy smokers did not demonstrate a statistically significant impact of the Pi-MZ phenotype on spirometry (*157*).

Genetically controlled antioxidant defense systems may also play an important role in determining susceptibility, both to free radicals released by inflammatory cells and to oxidants inhaled from the environment. The lungs possess several antioxidant defense mechanisms, including the reducing capabilities of iron and other metals, nonenzymatic antioxidants (including vitamins E and C), and the enzymatic scavengers (including glutathione thiol, superoxide dismutase, and microsomal epoxide hydrolase), which are under genetic control. The observations that the enzymatic antioxidants are under genetic control and that allelic variation alters their abilities to reduce free radicals (*213,214*) suggest that genetic factors may place some persons at greater risk for oxidant injury. There is currently no direct evidence, however, that specific genes related to antioxidant defenses interact with environmental factors to cause COPD.

Atopy, a genetically controlled trait, may lead to airway inflammation and asthma in genetically predisposed persons who are exposed to environmental aeroallergens. Asthma, in turn, appears to be a risk factor for the development of irreversible airflow obstruction that may ultimately be classified as COPD. Asthma, as well as airways hyperreactivity in the absence of asthma, has been associated with an accelerated rate of decline in FEV_1 (*215–218*), even after controlling for tobacco use. Although asthma and COPD are pathologically distinct (*219*), chronic asthma may lead to some histopathologic changes resembling COPD, including inflammation with epithelial cell loss, squamous metaplasia, leukocyte infiltration, basement membrane thickening (*220*), as well as parenchymal destruction. The irreversible changes in airway histology seen in chronic asthma are often referred to as "airway remodeling" (*221*). In addition, the radiographic (*222*) and physiologic (*223,224*) changes of emphysema have been noted in nonsmoking chronic asthmatics. Chronic asthma can result in fixed airways obstruction with loss of elastic recoil and expiratory flow, and with increased total lung capacity. Although asthma is frequently associated with an increased diffusion capacity (*224–229*), a reduction in diffusing capacity has also been noted in patients with no radiographic evidence of emphysema but who have severe small airways disease (*230*). Nonasthmatics with evidence of allergy to common aeroallergens have been reported to have a more rapid rate of longitudinal decline in pulmonary function (*216,218,231*), although conflicting data have been reported (*232*). In addition, one report suggests that exposure of sensitized persons to indoor allergens may result in accelerated longitudinal lung function decline even in the absence of asthma (*218*). The mechanisms by which asthma, airways hyperreactivity, and atopy lead to irreversible airways obstruction remain to be determined, although chronic airway inflammation provoked by environmental allergens and the structural consequences of this inflammation appear likely to play an important role. The genetic mechanisms of atopy and asthma are currently the focus of intensive investigation, and are beyond the scope of this review.

Conclusion

Although tobacco smoking has been recognized as the major environmental cause of COPD for nearly half a century, the elimination of this habit has been elusive. In addition, other environmental causes of COPD, such as occupational dust exposure, have been recognized. Although our understanding of the cellular and biochemical pathogenesis of COPD remains rudimentary, it is increasingly evident that the host response to environmental factors is subject to genetic variation. The example of API deficiency provides a clear example of the potential importance of gene–environment interaction in the pathogenesis of COPD, and the search for additional gene products influencing COPD risk is an area of active investigation. However, API deficiency is the only known single gene deficiency that results in COPD; more commonly, it appears these host responses to environmental stressors are under polygenic control.

Further research into the role of gene–environment interaction in the development of COPD must focus on several levels. Improving our understanding of the molecular mechanisms causing COPD will allow identification of possible target genes. Family studies with linkage analysis and investigation of gene–environment interactions may lead to the discovery of genetic polymorphisms that influence the risk of developing COPD.

The elucidation of response mechanisms may permit the identification of high-risk persons who should be targeted for intensive smoking-prevention or -cessation efforts and who should avoid other environmental risk factors. In addition, understanding these mechanisms may lead to the development of therapies that either alter the expression of genes or augment or inhibit gene products to reduce COPD risk. One example of such a therapy, augmentation therapy with purified human API for patients with severe API deficiency, has already been developed; future research may lead to new preventative therapies applicable to a larger proportion of persons who are at risk. The total elimination of tobacco smoking, of course, must remain the primary public health focus for the prevention of COPD.

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